Case Report

Late solitary metastasis of chromophobe renal cell carcinoma in the residual ureter

Yusuke Hakozaki, Kanako Matsuoka, Tomoyuki Koguchi, Junya Hata, Yuichi Sato, Hidenori Akaihata, Masao Kataoka, Soichiro Ogawa, Motohide Uemura and Yoshiyuki Kojima

Department of Urology, Fukushima Medical University School of Medicine, Fukushima, Japan

Abbreviations & Acronyms
chRCC = chromophobe renal cell carcinoma
CT = computed tomography

Correspondence: Yusuke Hakozaki M.D., Department of Urology, Fukushima Medical University School of Medicine, 1 Hikarigaoka, Fukushima 960-1295, Japan. Email: urohako@fmu.ac.jp

How to cite this article: Hakozaki Y, Matsuoka K, Koguchi T *et al*. Late solitary metastasis of chromophobe renal cell carcinoma in the residual ureter. *IJU Case Rep*. 2025; 8: 154–157.

Received 19 August 2024; accepted 13 January 2025. Online publication 24 January 2025

Introduction: Postoperative recurrence of chromophobe renal cell carcinoma is rare, and its metastatic process remains unclear. We here report a case of a solitary metastasis in the residual ureter detected 9 years after the primary surgery and discuss its possible recurrence mechanism based on our immunohistochemical study.
Case presentation: A 67-year-old woman received nephrectomy for a left renal tumor, which was diagnosed as chromophobe renal cell carcinoma with urinary collecting system invasion. Nine years postoperatively, a tumor was found in the residual ureteral stump and was surgically excised. The recurrent tumor was histologically diagnosed as chromophobe renal cell carcinoma surrounded by normal urothelial cells. On immunohistochemical staining, the tumor cells showed a high expression of uroplakin-2, a urothelium-specific marker.
Conclusion: In our case, highly adhesive uroplakin-2-positive cancer cells spilled from the primary site and attached to the residual ureteral stump, growing slowly while being gradually covered by normal urothelial cells.

Key words: late metastasis, renal cell carcinoma, residual ureter.

Keynote message

We presented late solitary metastasis of chromophobe renal cell carcinoma in the residual ureter. Uroplakin-2 may have contributed to the characteristic metastasis in our case.

Introduction

ChRCC accounts for approximately 4–6% of all types of RCC and has a good prognosis with a metastasis rate of 6–7%,[1] resulting in limited understanding of its recurrence mechanism. We present a case of residual ureteral metastasis of chRCC and discuss its possible metastatic mechanism suggested through immunohistochemical analysis of the primary and metastatic sites.

Case presentation

A 67-year-old woman was found to have a renal tumor through ultrasound screening. Contrast-enhanced CT showed a 72-mm left renal tumor adjacent to the renal pelvis (Fig. 1a). The tumor was not a typical clear cell RCC as it showed no enhancement in the arterial phase (Fig. 1b), but showed slight peripheral enhancement in the portal venous phase (Fig. 1c). The patient underwent laparoscopic left nephrectomy, and postoperative pathological findings revealed chRCC with urinary collecting system invasion (pT3aN0M0). Gross hematuria appeared 6 years after surgery and cystoscopy showed blood drainage from the left residual ureteral orifice, but contrast-enhanced CT and retrograde pyeloureterography showed no abnormal findings. In addition, urine cytology and left ureteral washing cytology were negative. Therefore, the patient was closely followed up every 3 months, and no recurrence was observed. At 9 years postoperatively, contrast-enhanced CT revealed a 10-mm mass in the left residual ureter (Fig. 2a). Retrograde pyeloureterography showed a filling defect in the residual

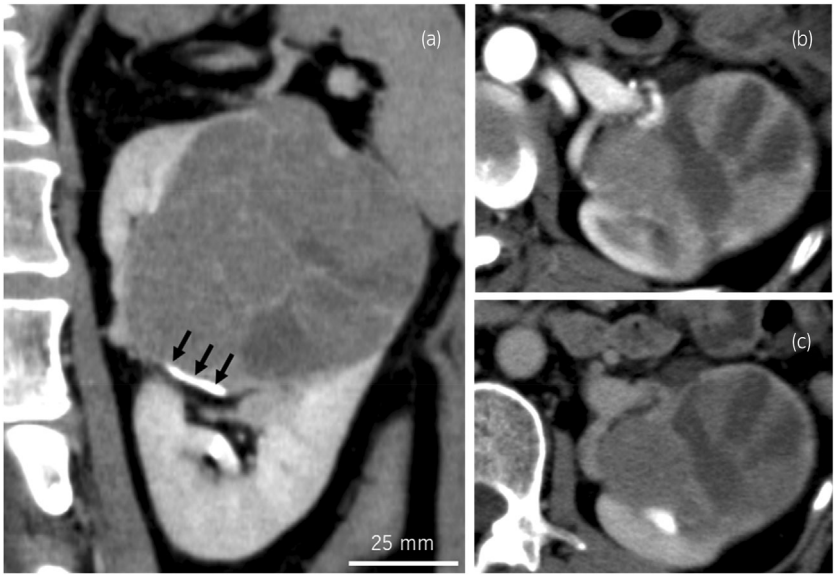

Fig. 1 Contrast-enhanced CT scans of renal tumor. Delayed phase (a), arterial phase (b), and late portal phase (c). A substantial 72-mm mass was observed in close proximity to the renal pelvis (a, black arrows) in the upper pole of the left kidney. The mass showed no enhancement in the arterial phase (b).

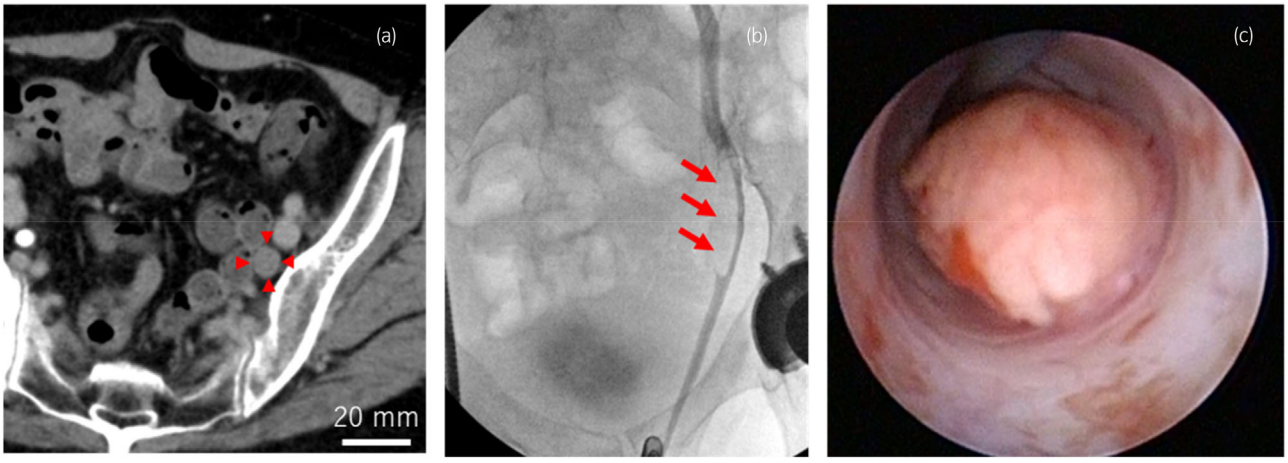

Fig. 2 Contrast-enhanced CT, retrograde pyeloureterography, and ureteroscopy for the left residual ureter 9 years postoperatively. Contrast-enhanced CT scan showed a 10-mm mass (red arrow heads) in the left residual ureter (a). Retrograde pyeloureterography showed a filling defect in the residual ureter (b, red arrows), and ureteroscopy identified a neoplastic lesion in the same area (c).

ureter (Fig. 2b), and ureteroscopy identified a neoplastic lesion in the same area (Fig. 2c). The residual ureter was surgically totally excised and histologically diagnosed as chRCC. It was localized between the mucosa and smooth muscle, without muscular or vascular invasion (Fig. 3a,b). As of the time of writing this manuscript, no recurrence has been observed for 5 years since this second surgery in 2019.

Immunohistological study

In order to understand the metastatic mechanism, we performed an immunohistological study. The cells surrounding the tumor were positive for uroplakin-2, a urothelium-specific protein, indicating they were urothelial cells (Fig. 3c,d). Tumor cells of both the primary and metastatic sites were also positive for uroplakin-2 (Fig. 4a,b). Given the slow recurrence of the tumor, we hypothesized the expression of tumor suppressor genes may be different in the primary and metastatic sites. To investigate this, we conducted immunohistochemical evaluation of the expression of tumor suppressor genes, PTEN and ARD1A, both of which were negative in the primary site (Fig. 4c,e), but positive in the metastatic site (Fig. 4d,f).

Discussion

ChRCC is a rare pathology and has an excellent prognosis with a 5-year survival rate of 83.9%.[2] Furthermore, solitary metastasis of RCC to the urinary tract is uncommon.[2] To the best of our knowledge, there have been only two reported cases of chRCC metastasis to the urinary tract: one to the residual ureter and the other to the bladder.[2,3] In general, RCC metastasis in the urinary tract is assumed to occur due to seeding of tumor cells in a metastatic site, followed by subsequent growth, but its mechanism has not been fully studied. Therefore, we investigated metastatic mechanisms using an immunohistological approach.

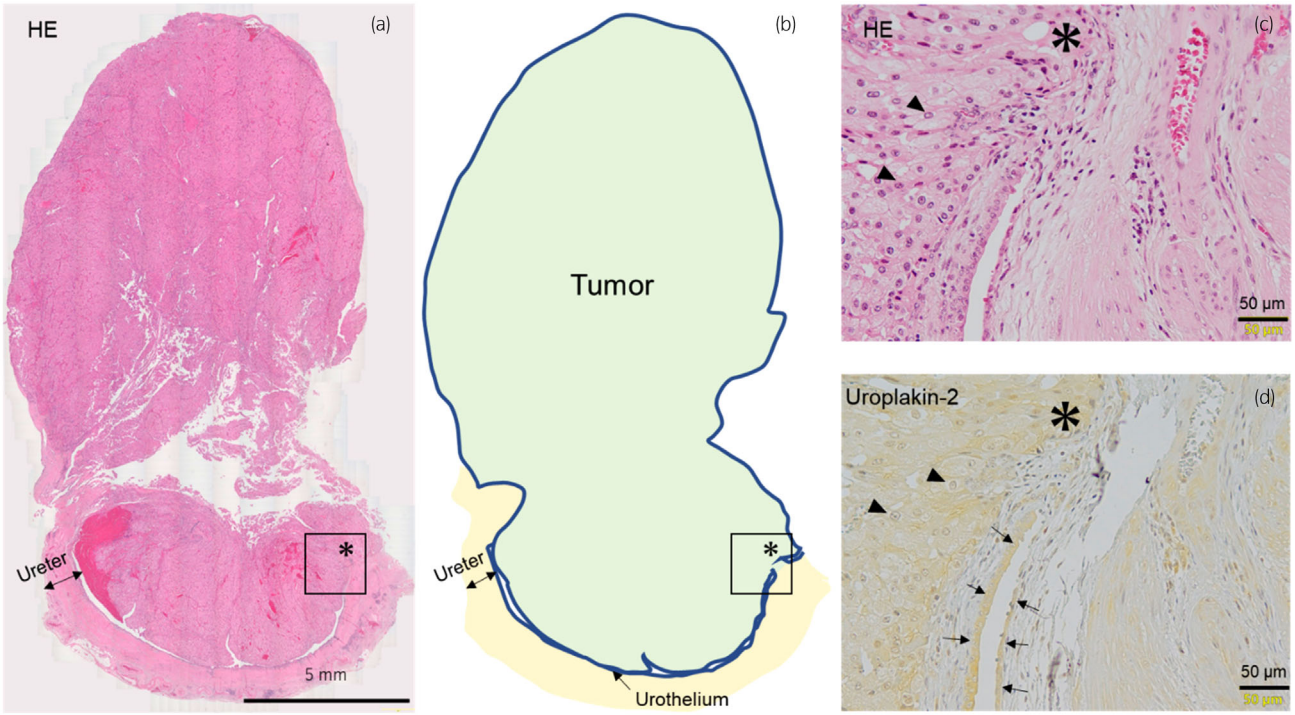

Fig. 3 Macroscopic and histopathological images of the metastatic site. A macroscopic view of the tumor (a). Schematic illustration of the tumor (green) covered by the urothelium (blue line) (b). The tumor is present in the ureteric cavity, extending from the ureteric wall (asterisk). The metastatic tumor cells were positive for uroplakin-2 (black arrow heads) (c). In addition, the surface of the metastatic tumor is covered with uroplakin-positive urothelial cells (black arrows) (d). Original magnification, ×200.

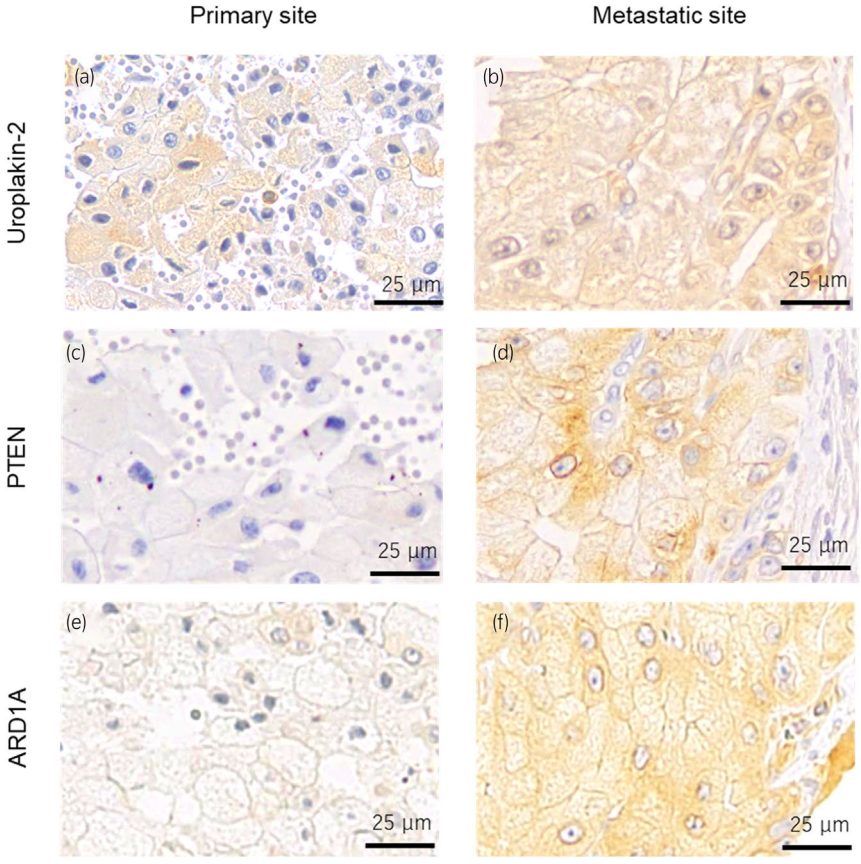

Fig. 4 Immunostaining images of the primary and metastatic sites. Immunohistochemistry of uroplakin-2 (a, b), PTEN (c, d), and ARD1A (e, f) in the primary site (left column) and metastatic site (right column). Both the primary and metastatic sites were positive for uroplakin-2 (a, b). PTEN and ARD1A were negative in the primary site (c, e) but positive in the metastatic site (d, f). Original magnification, ×400.

We focused on two distinctive characteristics of the metastasis in the present case: the slow speed of its growth and the uroplakin-2 positive cells covering the recurrent tumor. Although chRCC is generally known to progress slowly, the recurrent tumor in our patient took 9 years to be detected, leading us to suspect the involvement of tumor suppressor genes. PTEN is frequently found mutated in various types of tumors and the decrease of PTEN expression is associated with progression of chRCC.[4] ARD1A is a multifunctional protein required for various cellular activities, such as proliferation, differentiation, autophagy, and apoptosis, and has been reported to inhibit cancer growth.[5] Although neither PTEN nor ARD1A expression was detected in the primary site, we speculated there may have been a small number of PTEN- and ARD1A-positive cells in the primary site, which was predominantly negative for PTEN and ARD1A. The PTEN- and ARD1A-positive cells might have leaked into the renal pelvis and grew there, leading to the slow progression in this case. However, this was focused on tumor heterogeneity, which is the remit of the present study.

The other feature is the tumors were covered by uroplakin-2-positive cells. Miki *et al*. reported 43 cases of bladder metastasis from RCC, including two types of metastasis to the urinary tract: hematogenous metastasis and direct invasion.[6] In cases of hematogenous metastasis in RCC, cancer cells may spread to organs other than the urinary tract through systemic circulation. However, our patient had a single metastasis in the ureter, and there was no evidence of tumor invasion into blood vessels or muscle layers in the metastatic site. On the other hand, given that the primary chRCC had invaded the renal pelvis, we suspect direct invasion occurred due to the cells spilled from the renal pelvis and adhered to the urothelium. This is consistent with the well-known "seed and soil theory", which suggests the concept of organ specificity for tumor growth.[7] The chRCC tumor cells in the present case may have preferred the urothelial environment. Uroplakin-2 produced by urothelial cells is involved in intercellular adhesion and forms plaques, which act as a barrier protecting the urothelium. Uroplakin-2 may have been involved in the tumor cells in this case preferring the urinary tract environment. In the present case, both primary and metastatic chRCC expressed uroplakin-2, suggesting the tumor cells adhered to the urothelium due to the presence of uroplakin-2 and the urothelium regenerated on the tumor surface.

Based on the above analyses, we conclude the characteristic metastasis occurred through the following mechanism: the urothelium acquired its barrier function through the plaques formed by uroplakin-2; these plaques contributed to repelling most tumor cells from the urothelium, whereas uroplakin-2-positive tumor cells adhered to the plaque on the urothelium. The high affinity of uroplakin-2-positive tumor cells enabled the tumor cells to persist on the urothelium, leading to their growth in that location. In addition, the recurrent tumor cells expressed PTEN and ARD1A, which have tumor suppressive ability, and therefore grew slowly. We consider these two factors contributed to the characteristic metastasis in our case: Tumor cells grew slowly on the urothelium, where normal urothelial cells started and continued to cover the tumor during its slow progression made possible by tumor suppressor genes. As this report describes only one patient, further studies are needed to confirm our conclusion.

Acknowledgments

The authors thank the patient for consenting to the publication of this case report.

Author contributions

Yusuke Hakozaki: Conceptualization; data curation; investigation; project administration; resources; software; validation; writing – original draft; writing – review and editing. Kanako Matsuoka: Conceptualization; writing – original draft. Tomoyuki Koguchi: Conceptualization; formal analysis; investigation; methodology; project administration; supervision; writing – review and editing. Junya Hata: Supervision. Yuichi Sato: Supervision. Hidenori Akaihata: Conceptualization; data curation; formal analysis; project administration; supervision. Masao Kataoka: Supervision. Soichiro Ogawa: Supervision. Motohide Uemura: Supervision. Yoshiyuki Kojima: Supervision.

Conflict of interest

The authors declare no conflict of interest.

Approval of the research protocol by an Institutional Reviewer Board

Not applicable.

Informed consent

Informed consent was obtained from the patient.

Registry and the Registration No. of the study/trial

Not applicable.

References

1 Stec R, Grala B, Maczewski M *et al*. Chromophobe renal cell cancer-review of the literature and potential methods of treating metastatic disease. *J. Exp. Clin. Cancer Res.* 2009; **28**: 134.
2 Nitta S, Suetomi T, Kojou K *et al*. Solitary bladder metastasis of chromophobe renal cell carcinoma. *Hinyokika Kiyo* 2016; **62**: 63–7.
3 Macleod R, Kheirandish P, Ondego C, Biyani CS. Chromophobe renal cell carcinoma recurrence in the ureter. A late presentation of a rare metastasis. *Can. J. Urol.* 2015; **9**: E687–9.
4 Ricketts CJ, De Cubas AA, Fan H *et al*. The cancer genome atlas comprehensive molecular characterization of renal cell carcinoma. *Cell Rep.* 2018; **23**: 313–26.
5 Kim SM, Ha E, Kim J, Cho C, Shin SJ, Seo JH. NAA10 as a new prognostic marker for cancer progression. *Int. J. Mol. Sci.* 2020; **21**: 8010.
6 Miki M, Soga N, Masui S *et al*. A case of bladder metastasis of renal cell carcinoma. *Hinyokika Kiyo* 2012; **58**: 231–5.
7 Paget S. The distribution of secondary growths in cancer of the breast. *Lancet* 1889; **133**: 571–3.

